Pharmacokinetics considerations in the treatment of hypertension in risperidone-medicated patients

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Background

The prevalence of cardiovascular diseases including arterial hypertension in patients with severe mental illnesses such as schizophrenia has been consistently reported to be pronounced compared to the general population [1,2]. Despite the lack of a widely accepted underlying pathophysiological mechanism, the need for effective treatment of these comorbidities remains unmet, often ending up in polypharmacy. Hence, the risk of adverse drug-reactions mediated by alterations in cytochrome P450 (CYP) enzymes' activity can increase remarkably. Knowledge about drug-drug interactions is essential to enhance tolerability in the treatment of the psychiatric disease as well as in the treatment of the somatic disease.

Risperidone (RIS) is a second generation antipsychotic, a cytochrome (CYP) 2D6-catalyzed 9-hydroxylation leads to the major active metabolite, 9-hydroxyrisperidone (9-OH-RIS). Increasing in vitro and in vivo findings support an involvement of CYP3A4 and CYP3A5 in the RIS metabolism.

Amlodipine is a dihydropyridine calcium channel blocker (CCB), mainly metabolized in the liver, mainly by CYP3A4. Ramipril, on the other hand, belongs to angiotensin-converting enzyme (ACE) inhibitors and its elimination follows a rapid hepatic hydrolysis producing a major metabolite, ramiprilate.

Aim of the study was to analyse the *in vivo* pharmacokinetic interaction potential between RIS and first-line antihypertensive agents such as amlodipine and ramipril based upon therapeutic drug monitoring (TDM) under naturalistic conditions.

Methods

The present study is a retrospective analysis of data that were collected as part of a cooperation between the Department of Psychiatry, Psychotherapy and Psychosomatics of RWTH Aachen University Hospital, Aachen, Germany, and the Department of Psychiatry and Psychotherapy at the University of Regensburg, Germany between 2005 and 2015 as part of the clinical routine in both institutions and as part of the AGATE, (Arbeitsgemeinschaft Arzneimittelsicherheit bei psychischen Erkrankungen) (www.amuep-agate.de). The TDM database contained plasma concentrations of RIS and 9-OH-RIS of 2,293 adult risperidone medicated patients. Out of the initial sample we considered a group under concomitant medication with amlodipine (R_A, n=26), a group of patients under concomitant medication with Ramipril (R_R, n=25) and a risperidone monotherapy group (R_0, control group, n=832). Histograms yielded evidence of non-normal distributions, so that plasma concentrations, dose-adjusted plasma concentrations (C/D) of RIS, 9-OH-RIS and active moiety (RIS+9-OH-RIS; AM) as well as the metabolic ratios (MR) were compared pairwise between the groups by conducting a non-parametrical Mann Whitney U-test (MWU) with a significance level of 0.05. The demographic data of the two groups are presented in table 1.

Table 1

Group	number	age (years, ±SD)	gender (females %)	Dosage RIS (mg/day) (median, range)
R_0	821	40.8± 14.6	43.6	4.0 (1.0-10.0)
R_R	25	55.9 ± 13.7	64.0	6.0 (2.0-9.0)
R_A	26	61.5 ± 14.6	76.9	4.0 (1.0-8.0)

Results

Table 2 shows the medians and the ranges of plasma concentrations [in (ng/mL)] for RIS, 9-OH-RIS, and RIS + 9-OH-RIS as well as the metabolic ratios (MR) for each of the study groups. Table 3 shows the medians and the ranges of dose-adjusted plasma concentrations, C/D [(ng/mL)/(mg/day)], for RIS, 9-OH-RIS, and RIS + 9-OH-RIS for each of the three groups.

Table 2

Group	RIS [ng/ml]	9-OH-RIS [ng/ml]	AM [ng/ml]	MR
R_0	4.3 (0.1-224.0)	17.0 (0.3-196.5)	24.0 (1.8-264.0)	3.8 (0.04-290.0)
R_R	7.0 (1.2-165.0)	23.0 (1.4-100.0)	33.0 (2.8-213.0)	3.3 (0.29-15.0)
R_A	5.6 (0.3-67.0)	18.0 (4.5-49.0)	31.7 (6.7-112.0)	1.75 (0.23-56.67)

Table 3

Group	C/D RIS [(ng/mL)/(mg/day)]	C/D 9-OH-RIS [(ng/mL)/(mg/day)]	C/D AM [(ng/mL)/(mg/day)]
R_0	1.15 (0.02-74.67)	4.33 (0.08-42.0)	6.2 (0.5-88.0)
R_R	1.26 (0.39-27.5)	5.55 (0.7-16.67)	7.22 (1.4-35.5)
R_A	2.34 (0.15-16.75) ↑	5.75 (1.2-12.25) ↑	9.2 (2.0-28.0) ↑

The medians of risperidone daily dosages of the study groups showed no difference (p=0.214). The comparison of the pharmacokinetic parameters of RIS did not yield significant findings; p=0.124 for plasma and p= 0.438 for C/D levels of RIS, p=0.065 for plasma and p=0.279 for C/D 9-OH-RIS, p=0.092 for plasma and p=0.484 for C/D levels of AM, p=0.573 for MR.

We then compared the amlodipine group with control group; the median daily dosages did not differ (p=0.483). The MWU test revealed no significant differences for plasma levels of the parameters (p=0.057 for RIS, p=0.467 for 9-OH-RIS and p=0.195 for AM); metabolic ratios didn't differ between the groups as well (p=0.108). However, C/D levels of all parameters were higher in amlodipine patients than control group (p=0.011 for RIS, p=0.032 for 9-OH-RIS and p=0.002 for AM) (Fig.1, fig. 2).

Fig. 1

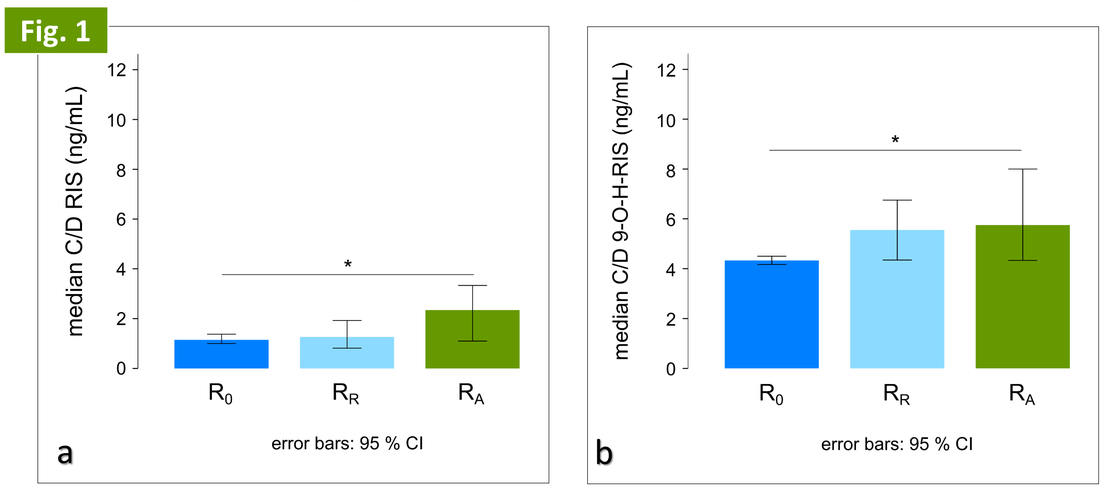
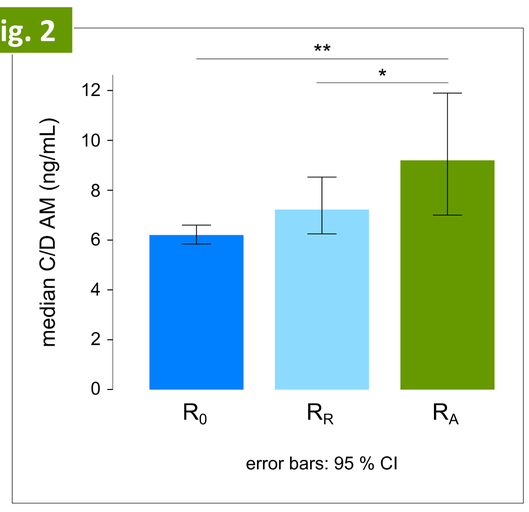


Fig. 2



Discussion

Clinical guidelines for the treatment of hypertension barely consider patients with SMI including schizophrenia and often neglect the potential of pharmacokinetic interactions. CCB and ACE inhibitors are among first-line antihypertensive agents [3]. Patients under a combination of RIS and amlodipine had higher C/D levels of RIS, 9-OH-RIS and AM compared to patients under risperidone monotherapy. Findings imply a potential inhibiting effect of amlodipine on RIS metabolism; this effect might be mediated by CYP 2D6. Contrastingly, pharmacokinetic parameters in patients under concomitant medication with ramipril didn't differ from the control group, implying no alterations in the disposition of RIS in patients co-medicated with ramipril. Thus, ramipril might show a comparative advantage in treatment of hypertension in RIS medicated patients; further research must validate this evidence.

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